



## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: Chaplin, et al.  
SERIAL NUMBER: 10/790,662 EXAMINER : Not Yet Assigned  
FILING DATE: March 1, 2004 ART UNIT : Not Yet Assigned  
FOR: COMPOSITIONS AND METHODS WITH ENHANCED  
THERAPEUTIC ACTIVITY

Mail Stop Amendment  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

### TRANSMITTAL LETTER

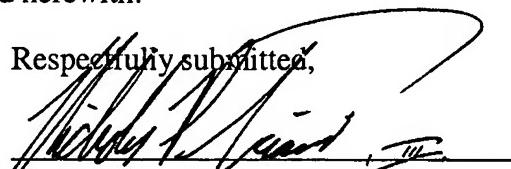
Transmitted herewith for filing in the present application are the following documents:

1. Information Disclosure Statement (1 page), in duplicate;
2. Modified Form 1449/PTO (2 pages), in duplicate;
3. Copies of Cited References: A1-7; B1-15; C1-26; and
4. Return Postcard.

If the enclosed papers are considered incomplete, the Mail Room and/or the Application Branch is respectfully requested to contact the undersigned at (617) 542-6000, Boston, Massachusetts.

The Commissioner is authorized to charge any fees that may be due, or to credit any overpayment, to the undersigned's account, Deposit Account No. 50-0311 Ref. No. 18217-519. A duplicate copy of this transmittal letter is enclosed herewith.

Respectfully submitted,



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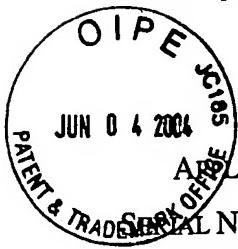
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Date: June 3, 2004



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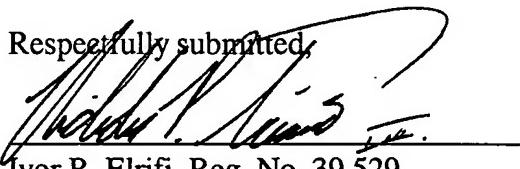
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## INFORMATION DISCLOSURE STATEMENT

Applicants make of record the documents listed on the attached modified Form PTO-1449 (submitted in duplicate) in the above-identified application.

This Information Disclosure Statement is being filed before the mailing date of a first Office Action based on the merits in the above-identified case. Accordingly, no fee or certification is believed required. Please charge any fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311 Reference No. 18217-519.

Respectfully submitted,



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Page 1 of 2  
Attorney Docket No.: 18217-519

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Modified Form 1449/PTO		Application Number	10/790,662
INFORMATION DISCLOSURE		Filing Date	March 1, 2004
STATEMENT BY APPLICANT		First Named Inventor	Chaplin
(use as many sheets as necessary)		Group Art Unit	Not Yet Assigned
		Examiner Name	Not Yet Assigned
		Attorney Docket Number	18217-519

**U.S. PATENT DOCUMENTS**

Exam Initials	Cite No.	U.S. Patent Document No.	Issue Date	Name of Patentee(s) or Applicant(s)	Class	Sub Class	Filing Date If Appropriate
	A1	5,079,257	01/07/92	Speckamp, et al.	514	312	
	A2	5,409,953	04/25/95	Pettit, et al.	514	464	
	A3	5,430,062	07/04/95	Cushman, et al.	514	646	
	A4	5,525,632	06/11/96	Obsumi, et al.	514	646	
	A5	5,567,786	10/22/96	Tseng, et al.	526	264	
	A6	5,674,306	10/07/97	Hatanaka, et al.	514	626	
	A7	6,423,753 B1	07/23/02	Dougherty	514	719	

**U.S. PUBLISHED APPLICATION DOCUMENTS**

Exam Initials	Cite No.	U.S. Published Application No.	Published Date	Name of Patentee(s) or Applicant(s)	Class	Sub Class	Filing Date If Appropriate

**FOREIGN PATENT DOCUMENTS**

Exam Initials	Cite No.	Foreign Patent Document Office Number	Name of Patentee(s) or Applicant(s)	Date of Publication	Translation Yes No
	B1	WO 92/16486	Aston Molecules Limited	10/01/92	
	B2	WO 99/02166	Angiogene Pharmaceuticals Ltd.	01/21/99	
	B3	WO 00/40529	Angiogene Pharmaceuticals, Ltd.	07/13/00	
	B4	WO 00/66528	Siil Biomedical Corporation	11/09/00	
	B5	WO 01/32210 A2	Pharmacyclics, Inc.; Univ. of Texas System	05/10/01	
	B6	WO 01/81355 A1	Arizona Board of Regents	11/01/01	
	B7	WO 02/02110 A1	Cancer Research Ventures Ltd.	01/10/02	
	B8	WO 02/04434 A1	Angiogene Pharmaceuticals Ltd.	01/17/02	
	B9	WO 02/08213 A1	Angiogene Pharmaceuticals Ltd.	01/31/02	
	B10	WO 02/12227 A2	AstraZeneca AB	02/14/02	
	B11	WO 02/14329 A1	Angiogene Pharmaceuticals Ltd.	02/21/02	
	B12	WO 02/49994 A2	Cancer Research Ventures Ltd.	06/27/02	
	B13	WO 02/50007 A2	Cancer Research Ventures Ltd.	06/27/02	
	B14	WO 03/035008 A2	OXiGENE, Inc.	05/01/03	
	B15	WO 03/040077 A1	Paterson Institute for Cancer Res.; The Univ. of Manchester Institute of Science and Technology	05/15/03	

**OTHER PRIOR ART – NON PATENT LITERATURE DOCUMENTS**

Exam Initials	Cite No.	Name of Author, Title (when appropriate), Publication, Volume, Page(s), Date, Etc.
	C1	Amaro, et al., "Metabolic activation of PCBs to Quinones: reactivity toward nitrogen and sulfur nucleophiles and influence of superoxide dismutase", <i>Chem. Res. Toxicol.</i> , 9:623-629 (1996).
	C2	Begleiter, A., "Clinical applications of quinone-containing alkylating agents", <i>Frontiers in Biosci.</i> , 5:e153-171 (2000).
	C3	Bolton, J. L., "Quinoids, quinoid radicals, and phenoxy radicals formed from estrogens and antiestrogens", <i>Toxicology</i> , 177:55-65 (2002).

	C4	Bui, et al., "Direct biocatalytic synthesis of functionalized catechols: a green alternative to traditional methods with high effective mass yield", <i>Green Chem.</i> , 2:263-265 (2000).
	C5	Bui, et al., "Direct biooxidation of arenas to corresponding catechols with E.coli JM109 (pDTG602). Application to synthesis of combretastatins A-1 and B-1", <i>Tetrahedron Lett.</i> , 43:2839-2841 (2002).
	C6	Fan, et al., "4-hydroxylated metabolites of antiestrogens, tamoxifen and toremifene are metabolized to unusually stable quinone methides", <i>Chem. Res. Toxicol.</i> , 13(1):45-52 (2000).
	C7	Faig, et al., "Structure-based development of anticancer drugs: complexes of NAD(P)H:quinone oxidoreductase 1 with chemotherapeutic quinones", <i>Structure</i> , 9(8):659-667 (2001).
	C8	Flowers-Geary, et al., "Cytotoxicity and mutagenicity of polycyclic aromatic hydrocarbon ortho-quinones produced by dihydrodiol dehydrogenase", <i>Chem. Biol. Interact.</i> , 99(1-3):55-72 (1996).
	C9	Gastpar, et al., "Methoxy-substituted 3-formyl-2-phenylindoles inhibit tubulin polymerization", <i>J. Med. Chem.</i> , 41: 4965-4972 (1998).
	C10	Gutierrez, P. L., "The metabolism of quinone-containing alkylating agents: free radical production and measurement", <i>Frontiers in Biosci.</i> , 5:d629-638 (2000).
	C11	Gutierrez, P. L., "The role of NAD(P)H oxidoreductase (DT-diaphorase) in the bioactivation of quinone-containing antitumor agents: a review", <i>Free Radic. Biol. Med.</i> , 29(3-4):263-275 (2000).
	C12	Ham, et al., "Mechanism of cell cycle arrest by menadione", <i>Bull. Korean Chem. Soc.</i> , 21(12):1173-1174 (2000).
	C13	Hill, et al., "Preclinical evaluation of the antitumor activity of the novel vascular targeting agent Oxi 4503", <i>Anticancer Res.</i> , 22:1453-1458 (2002).
	C14	Holwell, et al., "Anti-tumor and Anti-vascular effects of the novel tubulin-binding agent Combretastatin A-1 Phosphate", <i>Anticancer Res.</i> , 22:3933-3940 (2002).
	C15	Holwell, et al., "Combretastatin A-1 Phosphate a novel tubulin binding agent with <i>in vivo</i> anti-vascular effects in experimental tumors", <i>Anticancer Res.</i> , 22:707-712 (2002).
	C16	Li, et al., "Discovery and development of antimitotic agents that inhibit tubulin polymerisation for the treatment of cancer", <i>Expert Opin. Ther. Patents</i> , 12(11):1663-1702 (2002).
	C17	Pang, et al., "Simultaneous determination of etoposide and its catechol metabolite in the plasma of pediatric patients by liquid chromatography/tandem mass spectrometry", <i>J. Mass Spectrom.</i> , 36:771-781 (2001).
	C18	Pettit, et al., "Antineoplastic agents 429: Syntheses of the combretastatin A-1 and combretastatin B-1 prodrugs", <i>Anti-Cancer Drug Design</i> , 15:203-26 (2000).
	C19	Pettit, et al., "Antineoplastic agents 440: Asymmetric synthesis and evaluation of the Combretastatin A-1 probes (1S,2S)- and (1R,2R)-1,2-dihydroxy-1-(2',3'-dihydroxy-4'-methoxyphenyl)-2-(3", 4",5"-trimethoxyphenyl)-ethane", <i>J. Nat. Prod.</i> , 63:969-674 (2000).
	C20	Pettit, et al., "Antineoplastic agents 389: New syntheses of the combretastatin A-4 prodrug", <i>Anti-Cancer Drug Design</i> , 13:183-191 (1998).
	C21	Singh, et al., "Isolation, structure, and synthesis of combretastatin C-1", <i>J. Org. Chem.</i> , 54:4105-4114 (1989).
	C22	Sridhar, et al., "Amino acid adducts of PAH o-quinones: model studies with naphthalene-1,2-dione", <i>Tetrahedron</i> , 57:407-412 (2001).
	C23	Wardman, P., "Electron transfer and oxidative stress as key factors in the design of drugs selectively active in hypoxia", <i>Curr. Med. Chem.</i> , 8(7): 739-761 (2001).
	C24	Workman, P., "Enzyme-directed bioreductive drug development revisited: a commentary on recent progress and future prospects with emphasis on quinone anticancer agents and quinone metabolizing enzymes, particularly DT-diaphorase", <i>Oncol. Res.</i> , 6(10-11):461-475 (1994).
	C25	Yao, et al., "Synthesis and reactivity of potential toxic metabolites of tamoxifen analogues: droloxifene and toremifene o-quinones", <i>Chem. Res. Toxicol.</i> , 14(12):1643-1653 (2001).
	C26	Zhang, et al., "Synthesis and reactivity of a potential carcinogenic metabolite of tamoxifen: 3,4-dihydroxytamoxifen-o-quinone", <i>Chem. Res. Toxicol.</i> , 13(1):53-62 (2000).

A copy of this reference is not provided as it was previously cited by or submitted to the office in a prior application, Serial No. \_\_\_\_\_, filed \_\_\_\_\_, and relied upon for an earlier filing date under 35 U.S.C. §120 (continuation, continuation-in-part, and divisional applications).

Examiner Signature		Date Considered	
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EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.